

Chiral autocatalysis: reaction noise, micro-reversibility and chiral inhibition in mirror symmetry breaking

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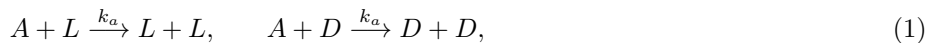
Applying the constraints dictated by the principle of detailed balance, we analyze a recent proposal for spontaneous mirror symmetry breaking (SMSB) based on enantioselective autocatalysis coupled to a linear decay of the enantiomers and in the presence of reaction noise. We find the racemic state is the final stable outcome for both deterministic as well as for stochastic dynamics, and for both well-mixed and small spatially-coupled systems. The racemic outcome results even when the autocatalytic cycles are driven irreversibly by external reagents, in manifestly non-equilibrium conditions. Our findings suggest that first-order autocatalysis coupled to reactions involving *non-linear* heterochiral dynamics is a necessary pre-condition for any mechanism purporting to lead to molecular homochirality.

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I. INTRODUCTION

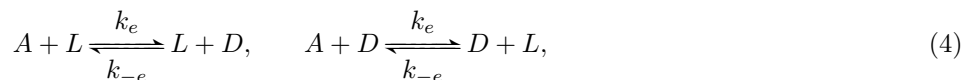
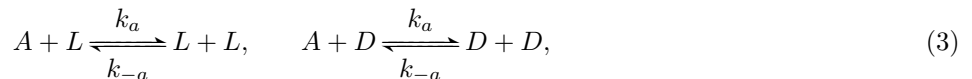
The observed bias in biopolymers composed from homochiral L-amino acids and D-sugars towards a single handedness or chirality is a remarkable feature of biological chemistry. Nowadays, there is a firm consensus that the homochirality of biological compounds is a condition associated to life that probably emerged in the prebiotic phase of evolution through processes of spontaneous mirror symmetry breaking (SMSB) [1]. This could have proceeded by incorporating steps of increasing complexity thus leading to chemical systems and enantioselective chemical networks [2, 3]. Theoretical proposals for the emergence of homochirality in abiotic chemical evolution, are based either on deterministic or on chance events [2, 3]. However, the current state of knowledge strongly suggests that the emergence of chirality must be based on reactions leading to spontaneous mirror symmetry breaking. SMSB are transformations yielding chiral outcomes as non-thermodynamic final stable states, and in the absence of any chiral polarization or external chiral physical forces [4]. This is provided by enantioselective autocatalysis, but not by the simple linear asymmetric induction reactions [5] on which past discussions on deterministic or chance phenomena were based for the justification of biological homochirality. Systems capable of SMSB lead to a stochastic distribution of final chiral signs between successive experiments. Nowadays this deterministic versus chance debate is restricted to more specific scenarios [1, 5, 9]. The SMSB abiotic scenario for the emergence of single homochirality in the biological world implies that single asymmetry emerges provided a small chiral fluctuation with respect to the idealized racemic state can be amplified [6] to a state capable of biotic evolution. Relevant features common to such systems are that they take into account the small fluctuations about the racemic state and that they display *non-linear* kinetic effects. These stochastic scenarios are theoretically well understood on general grounds [7, 8] and equally important, are experimentally feasible in the laboratory [9–11].

On the theoretical side, for describing systems capable of SMSB, the Frank model has been widely invoked to justify the emergence of biological homochirality [1, 3]. The original model [12] consists of an irreversible enantioselective autocatalysis Eq.(1) and an irreversible mutual inhibition reaction Eq.(2) between the product enantiomers, in an open-flow system:



This model has been extensively studied, allowing for reversible transformations and in diverse open-system scenarios [13]. The significance of the mutual inhibition step Eq. (2) is that it makes SMSB possible for first-order enantioselective autocatalysis, such as that of Eq. (1). Although enantioselective autocatalyses of quadratic and higher orders may by themselves lead theoretically to SMSB, they correspond to reactions of unrealistically high molecularity. For example, biological replicators of interest for enantioselective autocatalytic transformations, have their mechanisms composed by consecutive bi-molecular reactions. This means that, by themselves, these replicators *cannot amplify* the initial enantiomeric excess (*ee*). However, the coupling to a mutual inhibition reaction between the enantiomers can enable SMSB for some reaction and system parameters. Therefore, the chemically significant scenarios for the study of the emergence of chirality are those consisting of simple linear enantioselective autocatalyses coupled to reaction networks that include a mutual inhibition step.

Originally proposed as an alternative to the Frank model, the limited enantioselectivity (LES) model is composed of entirely reversible steps: an enantioselective autocatalytic reaction Eq.(3), a limited enantioselective autocatalysis Eq.(4), and direct production of enantiomers from an achiral precursor Eq. (5) [2]:



Note that the *inverse* reaction in Eq.(4) with rate k_{-e} provides the necessary chiral inhibition step, thus effectively replacing Frank's mutual inhibition Eq. (2) leading to the inert product P . The dynamic stability properties of racemic and chiral states in fully reversible versions of Frank and in LES, including hetero- and homo-dimerization, in both open and closed systems, are reported in detail in [14].

Typically, rate equation theory (in the mean field approximation) is used to cast chemical reaction schemes in terms of coupled differential equations for the temporal evolution of the concentrations of the chemical species involved.

In this deterministic kinetic dynamics, *initial conditions* must be taken to simulate the inherent statistical chiral fluctuations about the ideal racemic composition [15, 16]. In contrast, real chemical reactions are inherently stochastic in nature: the reagents in solution (or attached on surfaces) must encounter each other before they can react, and the probability per unit time for the reaction to occur is related to the corresponding reaction rate constant, which depends on the temperature. The molecular nature of chemical reagents and reactions gives rise to the concept of *intrinsic reaction noise*, and is typically multiplicative [17]. Despite the fact that stochastic and deterministic kinetics must coincide in the macroscopic limit (i.e., for large numbers of molecules), stochastic methods can be used to address the question of whether such internal noise affects the final outcome of the underlying reaction, and in what way it might do so. The answer to this question depends on the specific process studied. Thus, for example, reaction noise explains the anomalous scaling in reactions undergoing dynamic phase transitions from active to absorbing states [18].

The influence that reaction noise may have in schemes purporting to lead to SMSB is readily investigated. In the case of the Frank model with *reversible* autocatalysis (defined by the pair of Eqs.(3,2)), reaction noise induces complete chiral amplification starting from ideally racemic initial conditions in spatially extended domains, but this result requires the parameter $g \equiv \frac{k-a}{k_2}$, controlling the symmetry breaking transition, to satisfy the same condition as for the deterministic model, namely $0 \leq g < 1$ [19, 20]. That is, the *final outcome* of the reaction scheme is governed solely by this simple condition, irrespective of whether internal noise is included in the temporal evolution or not. On the other hand, neither chiral bias nor external physical chiral polarizations need be invoked to achieve homochirality when reaction noise is included [19]. Hence, the initial and subsequent chiral fluctuations intrinsic to the system [15, 16] are included automatically.

Stochastic methods are necessary to describe kinetic dynamics in the case of small volumes and/or small numbers of reacting molecules [21, 22], as is the case, for example, in compartmentalized cellular processes [23]. Therefore, the differences in the evolution of the *ee* between deterministic and stochastic kinetics should provide better insights regarding asymmetric inductions and SMSB processes in living systems. In this respect, internal noise has been considered recently in a closed-mass model which results from taking strictly irreversible enantioselective autocatalysis, Eq.(1) together with the direct production and decay of the enantiomers, Eq.(5) [24]. Stability analyses for the deterministic model show that the final stable state is necessarily racemic. Yet, the claim was made that reaction noise stabilizes the homochiral states, making these the most probable outcome of the system. According to this, in systems governed by stochastic kinetics, i.e., before coinciding with the limit of deterministic kinetics, the linear decay of the enantiomers to the compound A (Eq. (5)) is to play the role of mutual inhibition for achieving SMSB, i.e., the homochiral states are supposed to result without requiring additional “non-linearities” nor even chiral inhibition itself.

In this paper we analyze these claims in detail. As the need for chiral inhibition in SMSB has been questioned [24], we draw a careful distinction between linear racemization and non-linear mutual inhibition in Sec II A. The constraints dictated by detailed balance, often overlooked in the modeling of biological homochirality, are discussed in Sec II B. In Sec III we consider the influence, for both well-mixed and small spatially coupled systems, that reaction noise has on the stationary states of the chemical scheme when detailed balance is properly accounted for. In Sec IV we address the problem of coupling chemical reaction schemes to external energy sources for driving *unidirectional* cyclic reactions, a minimum requirement for biological systems. Conclusions are drawn in Sec V. Details of the calculation of the probability distribution for the enantiomeric excess are relegated to an Appendix.

II. CHIRAL INHIBITION AND MICROREVERSIBILITY

As the scheme in [24] (i) dispenses with chiral inhibition and (ii) overlooks the principle of detailed balance, we consider these two concepts below, bringing in some closely related reaction schemes for illustrative purposes.

A. Linear racemization and non-linear chiral inhibition

The Frank model [12] involves enantioselective autocatalysis coupled to a reaction between the two enantiomers of product/catalyst yielding an achiral addition product. The term “mutual chiral inhibition” was coined for this reaction because it represents the decrease of chiral compounds in a racemic ratio. This leads to an increase in the value of the enantiomeric excess *ee*. When this occurs faster than the reverse enantioselective autocatalysis, namely when $g \equiv \frac{k-a}{k_2} < 1$, a cooperative effect drives the amplification of the *ee* in the enantioselective autocatalysis: Eq.(1) or Eq.(3). As remarked above, in LES this mutual chiral inhibition is manifested via the inverse non-enantioselective autocatalysis, Eq.(4). Compared to Frank, in LES no inert product P nor achiral heterodimer is formed, but instead the recycling of one enantiomer back to the achiral precursor A plus the mirror image enantiomer. This reverse

reaction implies the disappearance of only one stoichiometric part of the racemic mixture (either D or L), but in the dynamics of the system there is a non-linear dependence on the heterochiral interaction $[L] \times [D]$, just as in the case of the mutual inhibition stage of Frank-like systems. The importance for SMSB of coupling enantioselective autocatalysis of first order (Eq.(1) or Eq.(3)) with such inhibition stages [Eq. (2) or Eq.(4)] is due to the fact that the autocatalysis *by itself* cannot yield SMSB. In lieu of these inhibitions, there is no amplification of chirality, and in the best of cases, (open flow systems, or systems with heterogeneous energy distributions, etc.), the production of chiral matter can only maintain the initial *ee* value. The significance of the heterochiral inhibition stage, when coupled to an enantioselective autocatalysis of first order, is that the overall reaction network is then able to lead to SMSB. This chiral state is a non-thermodynamic one, but is the more stable state of the system.

The reaction of Eq. (5), has been reported [24] as being able to play the role of the needed inhibition stage for SMSB in enantioselective autocatalysis of first order, by appealing to the presence of reaction noise. The character of such an inhibition stage, however, is easily appreciated by re-expressing it as follows:



The reactions of Eqs.(5,6) are identical and the direct transformation between enantiomers in Eq.(7) represents an equivalent overall transformation, as far as L and D are concerned. What actually differs between all three is the temporal or spatial resolution or scale at which we can resolve them into individual steps or else as overall, collective reactions. Thus the first, Eq.(5), describes two individual reactions, but because of the degenerate character of enantiomerism, the existence of one reaction implies necessarily the existence of the enantiomeric one. The second Eq. (6) is identical to (5), but it can also include a single reaction going through a non-stable intermediate, and the third Eq. (7) is a single reaction with no intermediate species made explicit. All these reactions are the basic transformations representing the chemical process known as “racemization”. The common effect of such reactions determines, in the case of closed systems with homogeneous energy distribution, that any initial *ee* value must decrease towards the unavoidable racemic mixture. Note that the three Eqs. (5-7) lead to the decrease the total chiral matter, but the underlying dynamics does not involve a non-linear dependence on the racemic composition [5]. This non-linearity is expressed in deterministic kinetics by the dependence on the product of the concentrations of both enantiomers, and in stochastic kinetics by the existence of a non-elastic heterochiral collision between the enantiomers.

B. Microreversibility

The rate constants in LES are constrained by the principle of microreversibility [14]:

$$\frac{k_a}{k_{-a}} = \frac{k_e}{k_{-e}} = \frac{k_n}{k_d}. \quad (8)$$

The LES model has had a controversial reputation in the past because the constraints dictated by microreversibility or detailed balance, have not always been correctly considered nor properly taken into account [14, 25]. Using Eq.(8) one proves that LES in a closed to mass flow system at uniform temperature cannot lead to either temporary nor permanent chiral symmetry breaking: the racemic state is the only stable outcome [14]. In order to overcome these microreversibility constraints necessarily requires extending the reaction model via coupling to external energy sources and/or to external reagents. The new reactions or energy fluxes thus introduced alter the overall set of (original) transformations and can allow for the (partial) lifting of the original microreversibility constraints. Thus for example, when the enantioselective and the limited enantioselective autocatalyses are individually *localized* within regions of low and hot temperatures, respectively, in a thermal gradient, mirror symmetry can be broken permanently [5, 26]. Alternatively, when the reverse reaction of the non-enantioselective autocatalysis is driven by an external reagent, LES in a uniform temperature can break mirror symmetry permanently [5, 27]. Both these modifications maintain LES far from equilibrium and also lift the constraints Eq.(8) on some of the reaction rates. Even so, this does not imply we can set any of the inverse rate constants to zero (and we cannot: doing so would violate Eq. (8)).

Artifacts in mathematical modeling can and do arise when (i) reactions are approximated by irreversible transformations and especially when (ii) irreversible and reversible reactions are combined *together* in the same scheme [25], as was done in [24]. Note that the original Frank scheme Eqs(1,2) involves only irreversible reactions (understood as approximations), but here there is no constraint dictated by microreversibility: in this case both rates k_1 and k_2 are

independent. The rates for the modified Frank model with reversible autocatalysis and mutual inhibition: Eqs. (3,2), are also independent.

In contrast, the individual rate constants for *reversible* autocatalysis in concert with reversible non-catalytic production must obey

$$\frac{k_a}{k_{-a}} = \frac{k_n}{k_d}. \quad (9)$$

We emphasize that, and as expressed by Wegscheider's rule [28, 29], the microreversibility constraint Eq. (9) requires us to include *both* forward and inverse chemical reactions in the autocatalysis Eq. (3), since direct production Eq. (5) is taken to be reversible in [24]. That is, one reaction is reversible if and only if the other one is. Thus, we cannot set $k_{-a} = 0$ in the presence of Eq. (5). If however, we insist on combining irreversible autocatalysis $k_{-a} = 0$ with irreversible direct production $k_d = 0$ [30], then the microreversibility constraint is satisfied consistently, and in the most trivial way, since

$$\frac{k_{-a}}{k_a} = \frac{k_d}{k_n}, \quad (10)$$

$$\Rightarrow 0 = 0, \quad (11)$$

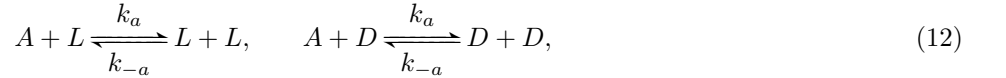
and we are free to vary the forward reaction rates k_n and k_a independently. But such an irreversible scheme [30] corresponds to reactions under strict kinetic control. On asymptotically long time scales, the inverse reactions become relevant and the closed mass system will necessarily racemize [31].

III. REACTION NOISE: ANALYTIC RESULTS AND SIMULATIONS

We consider the role of reaction noise in both well mixed and small spatially coupled systems when detailed balance is taken into account.

A. Stochastic model: well-mixed system

If we eliminate the reverse autocatalysis (set $k_{-a} = 0$) from the following reactions



we recover the scheme proposed in [24], which is itself a minor variation of the model in Ref. [30]. When this reverse step is overlooked, then the resultant reaction noise would appear to stabilize the homochiral states, provided a certain parameter $\alpha = V \frac{k_n}{k_a} \ll 1$. Here we include the obligatory reverse reaction as dictated by microreversibility, Eq. (9), and reconsider carefully the role of reaction noise on the stationary states of the system. In passing we note that the models considered up to this point are variations of either the basic Frank paradigm or of the LES model, obtained by combining some elements of the former with some elements of the latter, now taking reversible steps, or instead taking irreversible steps, etc.

We thus approximate the scheme Eqs. (12, 13) by means of a stochastic differential equation for the time dependence of the enantiomeric excess $\theta = \frac{[D] - [L]}{[D] + [L]}$. We consider a closed mass well-mixed system of volume V and total number of molecules N . Taking the limit, $N \gg 1$, as in [24], we arrive at the following equation for θ (see Appendix A):

$$\frac{d\theta}{dt} = -\frac{k_{-a}}{2 + \frac{k_{-a}}{k_a}} \left(\frac{N}{V} \right) \theta + \sqrt{\frac{k_{-a}}{2V} (1 - \theta^2)(2 - \theta^2)} \eta(t), \quad (14)$$

where $\eta(t)$ is Gaussian white noise with zero mean and unit variance.

The normalized stationary distribution of Eq. (14) is given by

$$P_s(\theta) = \frac{2^{1+b} \Gamma(b + \frac{1}{2})}{\sqrt{\pi} \Gamma(b) F(\frac{1}{2}, 1 + b, \frac{1}{2} + b; \frac{1}{2})} \frac{(1 - \theta^2)^{b-1}}{(2 - \theta^2)^{b+1}}, \quad \text{with} \quad b = \frac{N}{1 + \frac{k_{-a}}{2k_a}}. \quad (15)$$

We plot $P_s(\theta)$ for various values of b in Fig 1. The distribution $P_s(\theta)$ is *always* peaked around the racemic state $\theta = 0$ since the parameter $b \gg 1$. As the total number of molecules N increases, the distribution becomes ever more sharply peaked around $\theta = 0$. In particular, the probability for homochiral states $|\theta| = 1$ is strictly zero. The deterministic

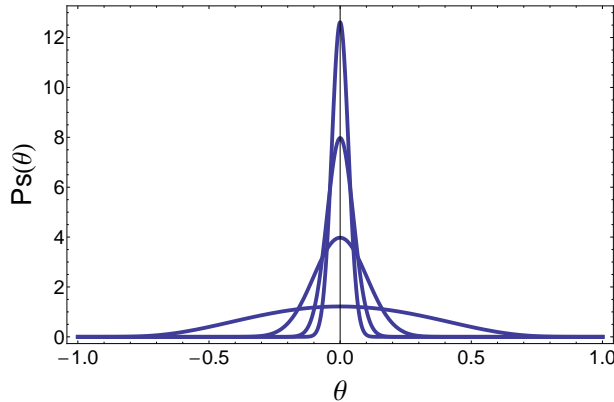


FIG. 1. Stationary probability distribution for the chiral order parameter, Eq. (15). Different values of $b = 10, 100, 400, 1000$ correspond going from the broadest to the narrowest distribution. $P_s(|\theta| = 1) = 0$ for homochiral states.

part of Eq.(14) has one fixed point at the racemic state $\theta = 0$, in accord with stability analyses for the deterministic kinetic rate equations. The amplitude of the noise is maximum for the racemic state, and vanishes at the homochiral states. Nevertheless, we cannot arrange for the noise amplitude to be larger than that of the deterministic term, since $b \gg 1$; see Eq. (15). This means that the racemic state is stable in the presence of reaction noise, and is surrounded by Gaussian fluctuations that become negligible for increasing total number N of molecules in the system, see Fig 1 and Fig. 2. As shown in Fig. 2, stochastic simulations of the scheme Eqs. (12,13) using the Gillespie

algorithm [32] reveal that the magnitude of the fluctuations about the racemic composition depend on the rate k_n . Thus we observe that the reaction noise is somewhat more erratic for $k_n = 0.1$ in comparison with the smoother fluctuations that result when $k_n = 10$. Note moreover the dependence of the total *chiral mass proportion*, defined as $([L] + [D])/([L] + [D] + [A])$: the fraction of total system mass which is chiral. Increased non-catalytic production leads to a greater proportion of chiral matter. The other rates were set to $k_a = k_d = 1$ as in [24], and we include $k_{-a} = 1/k_n$ as dictated by microreversibility. This implies that smaller k_n thus leads to a greater recycling of the enantiomers back to achiral precursor via reverse autocatalysis, leading to smaller net chiral matter than when k_n is large.

The racemizing tendency of the forward rate of non-catalytic production can also be appreciated in Fig 3 which shows the distribution in the enantiomeric excesses for different values of k_n . The greater the k_n , the more sharply peaked is the distribution about the racemic outcome; compare to Fig 1.

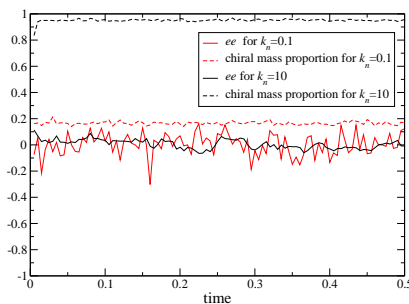


FIG. 2. Temporal series for the enantiomeric excess ee and the chiral mass proportion obtained from Gillespie simulations for different values of k_n (see legend). After a very brief transient, the curves fluctuate about the racemic state. The parameters are: $k_a = k_d = 1$ (and hence $k_{-a} = 1/k_n$), the number of molecules is 1000 (initial condition is 10 L, 10 D, 980 A). The ee is defined as $([L] - [D])/([L] + [D])$ and the chiral mass proportion as $([L] + [D])/([L] + [D] + [A])$.

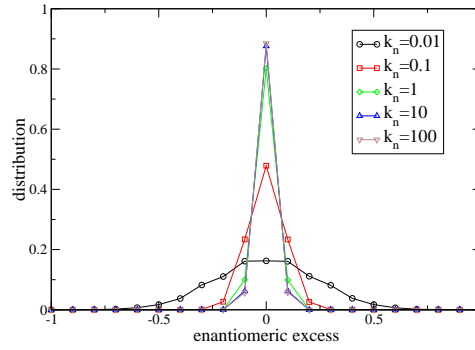


FIG. 3. Distribution of the enantiomeric excess ee obtained from Gillespie simulations for different values of k_n (see legend). After a brief initial transient, the distributions center about the racemic state. The parameters are: $V = 1$, $k_a = k_d = 1$ (and hence $k_{-a} = 1/k_n$), the number of molecules is 1000 (initial condition is 10 L, 10 D, 980 A). We obtain the $ee = ([L] - [D])/([L] + [D])$ at $T = 5$. We perform $R = 100000$ realizations. Binning is in intervals of 0.1 in the enantiomeric excess.

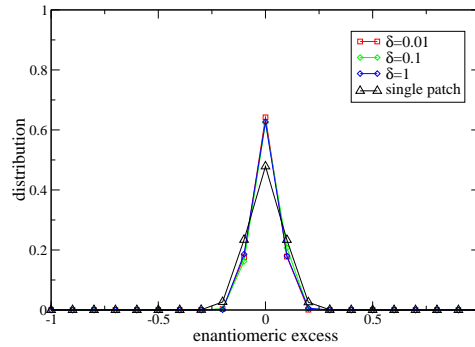


FIG. 4. The distribution of the total enantiomeric excess obtained from Gillespie simulations of a two-patch model for $k_n = 0.1$ and different values of δ (see legend). Asymptotically, the distributions center around the racemic state. The parameters are: $k_a = k_d = 1$ (and hence $k_{-a} = 10$), $V = 1$, the initial number of molecules per patch is 1000 (10 L, 10 D, 980 A) and we obtain the total enantiomeric excess $([L_1] - [D_1] + [L_2] - [D_2])/([L_1] + [D_1] + [L_2] + [D_2])$ at $T = 20$ and perform $R = 1000$ realizations. Binning is in intervals of 0.1 in enantiomeric excess. Spatial coupling applies to L, D, and A. For comparison, we show the distribution for a single uncoupled patch with $k_n = 0.1$ (100000 realizations).

B. Stochastic model: spatial coupling

The reaction scheme can be generalized and studied by spatially coupling a number of well-mixed systems. In the manner of [24], space can be discretized into a set of M patches of volume V , with the patches indexed by i . Here we consider such “spatial coupling” of $M = 2$ well-mixed patches. Within each such patch the reactions Eqs. (12,13) take place, with identical reaction rates for each patch, while all the molecules A_i, L_i, D_i can diffuse from one patch to the other, with a common spatial coupling constant δ (or, intra-patch “diffusion”):

$$A_i \xrightleftharpoons{\delta} A_j, \quad D_i \xrightleftharpoons{\delta} D_j, \quad L_i \xrightleftharpoons{\delta} L_j, \quad i \neq j \in (1, 2). \quad (16)$$

Stochastic simulations (Gillespie algorithm) indicate that each patch racemizes independently. The curves for the two patch system do not depend on the spatial coupling constant δ , see Fig. (4).

IV. UNIDIRECTIONAL IRREVERSIBLE CYCLES

In order to maintain an “irreversible self-replication”, the system in [24] would have to be driven by an external source of energy to maintain the steady state of the system far from equilibrium. This is a necessary, but not sufficient, condition for achieving SMSB. Additional effort is required to include explicitly such a hypothetical source as an integral part of the overall model, and then to demonstrate its feasibility. Indeed, perhaps the most challenging aspect of any proposal for modeling biological homochirality at the molecular level is not so much in the design of the intermediate reaction scheme itself, but rather in defining the very nature of the essential external energy source and its coupling to the reactions that comprise the intermediate chemical system.

The sought-after “irreversible self-replication” corresponds to a unidirectional cyclic reaction. But setting up such a cyclic reaction, by no means implies that the elementary autocatalytic reaction be “irreversible”, i.e., by simply putting $k_{-a} = 0$. The true cyclic behavior requires maintaining a steady unidirectional flow of matter in the system. This unidirectional cycling behavior is a general property of steady states maintained by an energy flux. A brief review of the meaning of *cycle*, using Onsager’s original “triangle reaction” as an example, [33] is warranted. Consider a closed mass system held at constant temperature, containing species A,B and C reacting according to the scheme:



At equilibrium there is no net flow around system since the forward and inverse reactions are in detailed balance($[\cdot]_{eq}$ denotes the equilibrium concentration):

$$k_1[A]_{eq} - k_2[B]_{eq} = k_3[B]_{eq} - k_4[C]_{eq} = k_5[C]_{eq} - k_6[A]_{eq} = 0. \quad (18)$$

The principle of microreversibility implies the following Wegscheider condition for the rate constants:

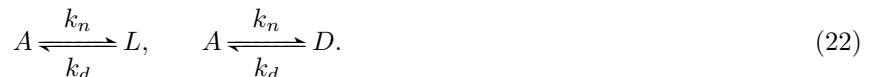
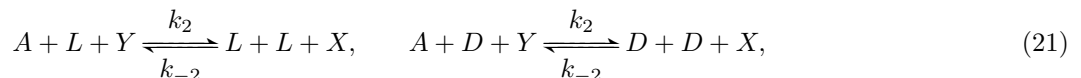
$$k_1 k_3 k_5 = k_2 k_4 k_6. \quad (19)$$

An external energy source could drive a net flow of material around the system, brought about by a flow of energy from a high potential source to a low potential sink, passing through the closed mass intermediate system of Eq.(17). The steady state condition would then require that

$$k_1[A] - k_2[B] = k_3[B] - k_4[C] = k_5[C] - k_6[A] = \mathcal{F} > 0, \quad (20)$$

where \mathcal{F} is the flow, the rate at which material is cycling around the system. This flow of material around a closed reaction loop is what is meant by a cycle [34]. Note that this cycle is irreversible: the net matter flow is unidirectional. We emphasize two important points: (i) Eq.(20) involves the non-equilibrium concentrations of the species involved, and (ii) the unidirectional matter flow \mathcal{F} depends on *all* the forward and reverse reaction rates k_i . The cycle is *not* established by simply putting the reverse rates to zero (this is prohibited by the Wegscheider condition Eq. (19)), but rather from an energy flow that traverses the closed mass system. By way of example, Morowitz offers a kinetic model for unidirectional cycles in Onsager’s network using photochemical reactions [34].

In Sec III, we demonstrated that the reaction scheme Eqs. (12,13) when obeying Eq. (9), does not lead to SMSB, regardless of the inclusion of reaction noise. We can legitimately circumvent this latter constraint by going to an out-of-equilibrium scenario. To assess whether irreversible cycling can lead to SMSB, we consider this scheme in a uniform temperature distribution driven by a constant concentration of external reactants, X and Y. See Eq. (21), an open system with X and Y matter exchange with the surroundings, and depicted in Fig 5. The resultant reaction network is cyclic one with permanent consumption and production of Y and X (or of X and Y, depending on the flow direction in the cycle):



It is straightforward to carry out a dynamic stability analysis for this system. The presence of external constant concentration reactants now lifts the constraint Eq. (9), and the far-from-equilibrium reaction model depends on the *two* independent parameters:

$$u = \frac{k_d}{k_n}, \quad g = \frac{k_{-2}[X]}{k_2[Y]}. \quad (23)$$

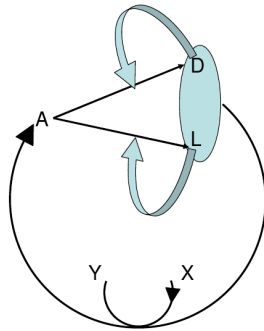


FIG. 5. The unidirectional cyclic network discussed in the text is composed of the *micro-reversible* reactions Eqs.(21, 22) in a uniform temperature distribution with Y and X matter exchange with the environment. A is an achiral compound and D and L the enantiomer pair of a chiral compound. The cycle is driven by the external reagents.

Because the reactants are external to the intermediate system, we can control the matter flow, e.g., in the forward sense, see Fig. 5:

$$k_2[A][Y] - k_{-2}[L][X] = \mathcal{F}_l > 0, \quad (24)$$

$$k_2[A][Y] - k_{-2}[D][X] = \mathcal{F}_d > 0. \quad (25)$$

$$(26)$$

The matter flow \mathcal{F}_{tot} is partitioned $\mathcal{F}_l + \mathcal{F}_d = \mathcal{F}_{tot}$, among the L or D autocatalytic branch of the reaction network, respectively. Nevertheless, even with the enantioselective autocatalyses driven *unidirectionally* in this way ($\mathcal{F}_l > 0, \mathcal{F}_d > 0$), a stability analysis proves that the racemic state is the only stable outcome, and for all $u, g > 0$.

By marked contrast, whereas detailed balance implies the racemic outcome for the LES model in a closed-mass system at uniform temperature, driving LES by external reagents can lead to SMSB [27]. The crucial fundamental difference between Eqs(21,22) and LES driven by external reagents [27] is in the inverse limited enantioselective catalytic step Eq.(4), which implies a *non-linear chiral inhibition* between the two enantiomers [35].

V. CONCLUDING REMARKS

The reaction models analyzed in this paper have served as useful vehicles for examining a number of basic issues relevant for framing proposals, coherent with fundamental chemical and physical principles, aimed at modeling biological homochirality at the molecular level. We summarize our main findings here. The following points are, to some extent, inextricably interrelated.

- **Detailed balance.** Thermodynamics dictates that the enantioselective autocatalysis and direct production/decay of the enantiomers must have identical ratios of the forward and reverse reaction rate constants, regardless of whether the system is in equilibrium or far from it. Once detailed balance is accounted for correctly, we have proven, by employing standard methods (stochastic differential equations, the Fokker-Planck equation) and numerical simulations, that the resultant model including reaction noise can never break chiral symmetry. On the contrary, the final stable outcome is always the racemic state. And, this holds whether the system is well-mixed or coupled spatially.
- **Reaction noise.** We have proven that the presence of reaction noise does not lead to any new final stable state not already in accord with the stability analysis of the deterministic model. Note: the regime where stochastic kinetics is expected to be important corresponds to the case of small volumes and *small* numbers N of molecules. In deriving our stationary probability distribution, we take the limit $N \gg 1$, as do the authors of Ref. [24]. In this limit, reaction noise has only a minor quantitative, but not qualitative, effect.

- **Chiral inhibition.** We have argued that the linear decay reaction of Eq.(5) cannot act as a mutual inhibition stage for SMSB when coupled to a first-order enantioselective autocatalysis. This strongly suggests, that a chiral inhibition reaction, or a set of coupled reactions generating a chiral inhibition dynamics, must have a *non-linear* chiral dependence [36], as is the case in both the LES and Frank models.
- **Irreversible cycles.** We have shown explicitly how to establish a unidirectional net flow of matter in the reversible autocatalytic reaction Eq.(21), by coupling it to external reagents. In spite of this, a stability analysis proves that the manifestly out-of-equilibrium model Eqs.(21,22) leads inexorably to the racemic state. And this result is intimately related to the absence of chiral inhibition.

There is a widespread and active research effort devoted to understanding the origins of biological homochirality that crosses the traditional boundaries between physics, chemistry and biology. The fundamental concepts treated here deserve careful consideration in scenarios for candidate reaction schemes proposed as models for the emergence of biological homochirality.

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Appendix A: Probability distribution for the enantiomeric excess θ

We cast the fully reversible kinetic scheme defined by Eqs. (12,13) in terms of stochastic differential equations to quantify the role played by internal reaction noise. The mapping of chemical reactions to master equations and then on to Fokker-Planck (FP) equations is an established technique [37, 38], as is the correspondence of FP with stochastic differential equations. Defining the state vector $\vec{x} = (x_1, x_2, x_3) \equiv (a, d, l)$ where a, d, l denote the time-dependent concentrations of molecules A, D and L, respectively, we find that our scheme may be approximated by the stochastic differential equation (defined in the Ito sense) [39]:

$$\frac{d\vec{x}}{dt} = \vec{H}(\vec{x}) + \mathbf{G}(\vec{x})\vec{\eta}(t), \quad (\text{A1})$$

where

$$\vec{H} = \begin{pmatrix} k_{-a}(d^2 + l^2) - a(2k_n + k_a(d + l)) + k_d(d + l) \\ -k_{-a}d^2 + a(k_n + k_ad) - k_d d \\ -k_{-a}l^2 + a(k_n + k_al) - k_d l \end{pmatrix}, \quad (\text{A2})$$

$$\mathbf{G} = \frac{1}{\sqrt{V}} \begin{pmatrix} \sqrt{k_{-a}d^2 + a(k_ad + k_n) + k_d d} & \sqrt{k_{-a}l^2 + a(k_al + k_n) + k_d l} \\ -\sqrt{k_{-a}d^2 + a(k_ad + k_n) + k_d d} & 0 \\ 0 & -\sqrt{k_{-a}l^2 + a(k_al + k_n) + k_d l} \end{pmatrix}, \quad (\text{A3})$$

and the η_j ($j = 1, 2$) are Gaussian white noises with zero mean and correlation, $\langle \eta_i(t)\eta_j(t') \rangle = \delta_{ij}\delta(t - t')$. V is the system volume. The rate of inverse autocatalysis is *not* an independent variable, but obeys the constraint:

$$k_{-a} = k_a \frac{k_d}{k_n}. \quad (\text{A4})$$

The number of chemical degrees of freedom \vec{x} can be effectively reduced from three to one [39]. This is so because firstly, the total number of molecules is conserved by our reaction scheme, thus so is the total concentration $n = a + d + l$. Secondly, the total chiral matter $\chi = d + l$ is a *fast degree of freedom* relative to the enantiomeric excess θ [20]. Simulations of the fully reversible scheme Eqs. (12,13) using the Gillespie algorithm [32] confirm that χ approaches a stable fixed point value surrounded by small Gaussian fluctuations (see, e.g., Fig 2). We therefore substitute $\chi(t) \rightarrow \chi^*$ into the equation for $\theta(t)$ derived below. We thus carry out the change of variables on Eq.(A1):

$$(a, d, l) \rightarrow (n, \chi, \theta) = (a + d + l, d + l, (d - l)/(d + l)), \quad (\text{A5})$$

employing Ito's formula [37]:

$$df(\vec{x}) = \left[\sum_i H_i(\vec{x}) \partial_i f(\vec{x}) + \frac{1}{2} \sum_{i,j} [\mathbf{G}\mathbf{G}^T]_{ij} \partial_i \partial_j f(\vec{x}) \right] dt + \sum_{ij} \mathbf{G}(\vec{x})_{ij} \partial_i f(\vec{x}) dW_j(t). \quad (\text{A6})$$

From Eq. (A6) it is straightforward to demonstrate that $\frac{dn}{dt} \equiv 0$ is identically zero, as it must be. From $\frac{d\chi}{dt} = 0$ we solve for the fixed point χ^* :

$$\chi^*(\bar{\theta}) = \frac{k_a n - 2k_n - k_d + \sqrt{(k_a n - 2k_n - k_d)^2 + 8nk_n[k_a + \frac{1}{2}(1 + \bar{\theta}^2)k_{-a}]}}{2k_a + (1 + \bar{\theta}^2)k_{-a}}, \quad (\text{A7})$$

Since $\chi \geq 0$, we take the positive root. Note the total chiral matter $\chi^*(\bar{\theta})$ depends *weakly* on the most probable stationary value $0 \leq \bar{\theta}^2 \leq 1$ for the chiral order parameter. The most probable value of $\bar{\theta}$ is determined from the stochastic differential equation for $\theta(t)$. We prove below that *self-consistency* requires taking $\bar{\theta} = 0$ in Eq. (A7).

We derive the stochastic equation obeyed by $\theta(t)$ and substitute $\chi^*(0)$ into this equation. We express the result in terms of the total number of molecules $N = Vn$ and for $N \gg 1$. The enantiomeric excess or chiral order parameter θ obeys the equation

$$\frac{d\theta}{dt} = -\frac{k_{-a}}{2 + \frac{k_{-a}}{k_a}} \left(\frac{N}{V} \right) \theta + \sqrt{\frac{k_{-a}}{2V}} (1 - \theta^2)(2 - \theta^2) \eta(t), \quad (\text{A8})$$

where $\eta(t)$ is Gaussian white noise with zero mean and unit variance.

From the Fokker-Planck equation corresponding to Eq (A8) we readily solve for the steady state probability distribution $P_s(\theta)$ for θ [38]. We find

$$P_s(\theta) = \mathcal{N} \frac{(1 - \theta^2)^{b-1}}{(2 - \theta^2)^{b+1}}, \quad \text{with} \quad b = \frac{N}{1 + \frac{k_{-a}}{2k_a}}, \quad (\text{A9})$$

and the normalization constant

$$\mathcal{N} = \left(\int_{-1}^1 d\theta \frac{(1 - \theta^2)^{b-1}}{(2 - \theta^2)^{b+1}} \right)^{-1} = \frac{2^{1+b} \Gamma(b + \frac{1}{2})}{\sqrt{\pi} \Gamma(b) F(\frac{1}{2}, 1 + b, \frac{1}{2} + b; \frac{1}{2})}, \quad (\text{A10})$$

where F is the hypergeometric function [40].

From P_s we conclude (see Fig 1) that the most probable value for the chiral order parameter is $\bar{\theta} = 0$, corresponding to the racemic state, thus establishing the self-consistency of employing this value in Eq. (A7).

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